REMARKS/ARGUMENTS

Claims 1, 2, and 5-47 are presently pending in this application. Claims 1, 2, and 31 are amended. Claims 46 – 47 are added.

No new matter has been added by the new claims. The amendment to claims 1, 2, and 31 changes only the syntax of the claims.

Support for claim 46 can be found in claim 1 as originally filed and in the examples of the present application. In particular for the linkage sites, linkage through both the S^1 site and at an aglycone oxygen if S^1 and/or S^2 is cleaved off are specifically recited in claim 1. S1 is disclosed as a linking site and therefore its deletion is supported. With regard to deletion of S^1 from the claims, it is noted that under the rules of practice, if alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. MPEP 2173.05(i) citing *In re Johnson,* 558 F2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977). Similarly, acetyl salicylic acid and aglycone compounds are recited in the original claim 1 and therefore can be disclaimed. Lastly, meclofenamic acid is recited in original claim 1 and so is a macrolide wherein Z is $-N(R_N)-$ and W is $-CH_2-$. Therefore, the disclaimers are appropriately supported.

Support for claim 47 can be found in the provisional application as filed, starting on page 9, line 4 to the end of page 12 for the macrolide and on page 13 starting at line 1 for the NSAID. Support for the term R^p and OR^p can be found in the provisional application on page 12 lines 1 – 13 as well as in the structural formulas for the macrolide sugar groups that encompass explicitly both hydroxyl and amine protective groups (pages 10-11). Support for the linkage at the C4' position on S^1 can be found in the provisional application page 18 line 23.

35 U.S.C. §102(a)

The Examiner has rejected claims 1, 2, 5-7 and 31-45 under 35 U.S.C§102 (a) as being anticipated by Burnet et al. (US 2004/0087517). The Burnet '517 application was filed on February 14, 2003 and claims priority to provisional application US 60/357,434, filed Feb. 15, 2002. It was published on May 6, 2004.

This rejection is respectfully traversed. The Burnet '517 application is not available under 35 U.S.C§102(a) against any of the pending claims since subject matter disclosed by Burnet

was not known or used by others in this country, or described in a printed publication in this or a foreign country, before the invention of claims 1, 2, and 5-47. Burnet '517 was published on May 6, 2004 after the filing date of the present nonprovisional application (July 7, 2003), therefore later than the present priority date (July 8, 2002), and there is no indication that the subject matter of Burnet '517 was known or used in this country before the claimed invention. Accordingly, no claim is anticipated by Burnet under 35 U.S.C. §102(a).

35 U.S.C. §102(e)

The Examiner has rejected claims 1, 2, 5-7 and 31-45 under 35 U.S.C§102 (e) as being anticipated by Burnet et al. (US 2004/0087517).

1. The present invention antedates Burnet

The priority date of the present application is July 8, 2002 based on provisional application 60/394,671. The priority document of the present application contains 16 actual examples and discloses the preparation of 16 conjugates that were reduced to practice no later than July 8, 2002. At least two conjugates (compounds 4-5) were made and characterized on or before February 15, 2002, the priority date that the Burnet application asserts and thus antedate any disclosure in the burnet nonprovisional application. The pre-February 15, 2002 synthesis and characterization of these compounds and the diligent synthesis and characterization of several other compounds are supported by the accompanying §1.131 declaration by Linda Tomašković, one of the inventors.

The early synthesis and characterization of these two compounds (Compounds 4 – 5, see testimony of and Exhibits B and C accompanying the Tomašković declaration) demonstrate that the present invention was at least conceived prior to February 15, 2002, and reduced to practice prior to February 15, 2002 and this activity continued and expanded thereafter until the provisional application was filed July 8, 2002. As filed, the provisional application contains 16 working examples (Examples 1-16), including 14 examples in addition to the two described in the declaration Exhibits B and C, each of which were synthesized prior to February 15, 2002. A further 7 compounds were synthesized prior to filing the nonprovisional. This demonstrates that the inventors diligently worked to synthesize and test additional conjugates from prior to February 15,

2002 until the filing of provisional application 60/394,671 and thereafter until the filing date of the present application.

Compounds of the present invention were understood to have anti-inflammatory activity. As provided in the Tomašković declaration and its Exhibit A, the assignee of the present application has had an on-going program addressing anti-inflammatory conjugates since before February 15, 2002. Conjugates having an "anti-inflammatory subunit that can be steroid or nonsteroid" (Declaration Exhibit A pg 4: 2-3) were developed by the assignee no later than January 3, 2002 for their anti-inflammatory activity. Therefore, the anti-inflammatory utility of compound such as those described in the present invention was contemplated prior to February 15, 2002.

2. Burnet Provisional fails to disclose the claimed compounds.

In addition, the Burnet application does not provide sufficient teachings to describe the conjugates of claims 1, 2, 5-7 or 31-45. According to the Burnet provisional application, a "transportophore" can encompass a variety of molecules, including broad classes of compounds such as alcohols and organic acids. Specifically, transportophores are described in the provisional Burnet specification at page 3 line 23 to page 4 line 2 as follows:

> The transportophore can be a metabolite (such as an amino acid or peptide), a natural product, a metabolite derivative (e.g., a sugar, amino, or peptide derivative), an organic acid an organic base, a nucleobase, or an alcohol. It can be an amphiphilic molecule having a pKa value of 6.5 to 9.5, or a cyclic or heterocyclic molecule (e.g., lactone, lactam, ether, cyclic acetal or hemi-acetal). The cyclic or heterocyclic molecule can have an attached sugar. The cyclic or heterocyclic molecule can be a macrolactone or macroether, including a macrolactone or macroether having an attached sugar. The cyclic or heterocyclic molecule can also be a macrolide or ketolide having an amino sugar, including a macrolide having mono-, di-, or tri-basic groups (e.g., an amine).

The largely functional characterizations above encompass countless molecules. For instance, although a "metabolite derivative" is exemplified in Burnet as "a sugar, amino, or peptide derivative," this language does little to narrow the scope of compounds included in its definition because "amino," for example, includes any compound having an $-NH_2$ group. The other types of listed transportophores are at least as broad as metabolite derivatives. A "natural product," for example, is seemingly limitless and could comprise any compound that is not synthetic. The term

"alcohol" is similarly wide-ranging and includes any alkyl compound containing a hydroxyl group. Likewise, an "organic acid" includes a vast number of compounds that contain carboxyl group(s). A similar comment can be made about the extensive breadth of the other types of transportophores quoted above as well.

Additionally, the term, "therapeutic agent," introduced in the Burnet provisional at page 31, lines 12-22, as follows:

> A "therapeutic agent," as used herein, is a molecule with pharmacological activity (e.g., a therapeutic agent, medicine, medicament, or active agent), a disease modification agent, or any other molecule that can be covalently attached to a transportophore via a bond or a linker which may have a desirable mode of action in immune cells.

The term "therapeutic agent" includes a myriad of compounds without limitation as to structure or pharmacological activity, or mechanism for exerting such activity. The provisional specification provides a long, yet "non-exclusive," list of classes of therapeutic agents on page 36 line 26 to page 40 line 16. Yet, these examples illustrate only a small number of therapeutic agents that could be coupled to an even smaller number of illustrated transportophores. For the reasons advanced above regarding the transportophore, this scanty description of therapeutic agents and scanty pairing of such agents with transportophores, is insufficient to circumscribe for a person of ordinary skill the group of conjugates included claims 1, 2, 5-7 and 31-45 or the present invention. There is simply no guidance, apart from the provisional applications 15 specific macrolide-NSAID conjugates and additional 8 conjugates in Burnet '517, as to which transportophores can be paired with which therapeutic agents, not to mention at which point on the molecule the former should be linked to the latter without destroying either the targeting ability of the transportophore or the therapeutic activity of the therapeutic agent. Although a reference may be relied upon for all that it would have reasonably suggested to one of ordinary skill in the art (MPEP 2123 citing *Merck & Co. v. Biocraft Laboratories,* 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert denied* 493 U.S. 975 (1989)), the vague broad and unfocused disclosure regarding the non-antibiotic therapeutic agent only exacerbates the insufficiency of the disclosure identified with respect to the transportophore.

In our view, the examples with their exemplification of a very narrow group of transportophores conjugated with the particular therapeutic agents do not provide support for the particular macrolides and NSAIDS provided in the claimed invention. The disclosure does not place a person of ordinary skill in possession of the subgenus of conjugates, in which the transportophore is suited to the non-antibiotic therapeutic agent, the point of linkage does not destroy function in one or the other.

The Burnet provisional application, in examples 2 – 35, contains 56 macrolide transportophore conjugates. There is no indication about what type of therapeutic agent can be conjugated to these macrolides other than the particular therapeutic agents described.

Lastly, the Burnet specification does not disclose the point of attachment between the linker and the transportophore and between the linker and the non-antibiotic therapeutic agent, other than by generally stating that the linker attaches through its "functional group"– a term that is nearly limitless in scope. Nor does the Burnet specification indicate where the point of attachment should be between the therapeutic agent and the transportophore in those conjugates that contain a bond in place of a linker.

Of the 56 macrolide conjugates exemplified in the Burnet provisional application, 33 of them contain a therapeutic agent attached through a sugar on a macrolide transportophore; 22 contains a therapeutic agent attached through a nitrogen atom attached to a macrolide ring; and one contains a therapeutic agent attached through a pendent oxygen atom attached to a macrolide ring.

In our view, the Burnet disclosure of only narrow groups of conjugates (out of the numerous possibilities encompassed by the scope of possible conjugates), and of a limited number of modes and sites of attachment of the transportophore to the therapeutic agent, does not provide sufficient teachings to anticipate the claims of the present invention.

Claim 1

Accordingly, Burnet does not anticipate claim 1 under 35 U.S.C. § 102(e) at least because the reference is removed by the showing of prior invention as discussed above.

The attached declaration by Linda Tomašković, provides for a conception and reduction to practice of the present invention prior to the filing of the Burnet provisional application. Exhibits B and C for this declaration are the pages of the laboratory notebooks (and their English translation) recording the synthesis and characterization (by mass spectrometry and HPLC) of two compounds made prior to February 15, 2002. These compounds (also identified in claims 11-12) are within the scope of claim 1. This evidence demonstrates that the Inventors had conceived and reduced the invention to practice before the Burnet provisional application was filed. Further, the scope of the provisional patent application as filed show further that the Inventors diligently worked on this invention, as declarant testifies, from conception to the filing of the provisional application.

We note that it is not necessary for the applicants to show reduction to practice of the entire scope of the invention. The §131 declaration "must establish possession of either the whole invention claimed or something falling within the claim (such as a species of a claimed genus), in the sense that the claim as a whole reads on it." MPEP 715.02 citing *In re Tanczyn* , 347 F.2d 830, 146 USPQ 298 (CCPA 1965).

Since the Burnet application was not filed before the present invention was conceived and reduced to practice, it is not available as a reference under 35 U.S.C. §102(e).

Claim 2

Since claim 1 is not anticipated, it follows that independent claim 2, which is narrower than but entirely within the scope of claim 1, is not anticipated either.

Claims 5-7

Since claim 2 is not anticipated, it follows that claims 5-7 dependent on claim 2, are not anticipated either.

Claims 8 - 30

These claims are not rejected under 35 U.S.C. §102.

Claim 31

Since Burnet does not anticipate the product claim as discussed above, the subject matter of claim 31, a process for making the novel conjugates of claim 1, is also not anticipated. In addition, the processes of claim 31 are not taught by Burnet. Burnet discloses mixing the therapeutic agent with linkers (e.g., succinic anhydride, glutaric acid, or carbonyldiimidazole) and then combining the transportophore (e.g., macrolide); this does not anticipate the present process.

Claims 32 and 39

Burnet does not anticipate the pharmaceutical composition claims 32 and 39 since the claimed pharmaceutical compositions are limited to compounds of claim 1, which are not anticipated as shown above, and to derivatives of such compounds also not anticipated by Burnet.

Claims 33-38 and 40 - 45

These claims are drawn to methods of using the product of claim 1 are not anticipated by Burnet at least for the reason that the product of claim 1 is not anticipated by Burnet.

Claim 46

Claim 46 is not anticipated by the Burnet '517 document, not only because it has been removed as a reference under 35 U.S.C. § 102(e) by the present showing of prior invention but also—and independently—because none of the specific macrolides in either the Burnet provisional application or in the Burnet '517 application are encompassed by this claim. Particularly, claim 46 does not read on compounds linked to the macrolide at the desosamine C-2' position, or the macrolide C-9=N position (Z is >C=N-R_M). Nor does claim 46 encompass macrolides linked at the 9a position when the NSAID is meclofenamic acid or ibuprofen. Similarly, claim 46 excludes macrolide conjugates linked through the desosamine C2' or C3' positions as well as macrolides linked through the C3 position wherein simultaneously D is acetylsalicylic acid.

Anticipation requires that each and every element of the rejected claim be disclosed in a single prior art reference. See, M.P.E.P. § 2131. Every element of the claimed invention must be literally present, arranged as in the claim. *Perkin Elmer Corp. v. Computervision Corp.*, 732 F.2d

888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984). A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Since each element of claim 46 is not disclosed in Burnet '517 or in the Burnet priority document, this claim would not be anticipated, even if the Burnet documents were available as references.

Claim 47

Claim 47 is similarly not anticipated by Burnet '517 under 35 U.S.C. § 102(e) because of the showing of prior invention, as described above.

Claim 47 is also independently not anticipated by Burnet '517 because the subject matter of Claim 47 was present in the provisional application filed July 8, 2002, (from which the present application claims priority). This filing date is prior to the filing date of Burnet '517. The Burnet provisional application has a filing date of February 15, 2002. However, no compound of the Burnet provisional application is encompassed by Claim 47.

Since claim 47 antedates the Burnet '517 reference, the Burnet '517 reference cannot be available under 35 U.S.C. § 102(e) and therefore could not anticipate claim 47 because it is entitled to an earlier filing date.

The Burnet provisional application, as discussed above, was filed before the priority date of the present application. However, Claim 47 does not encompass any compounds disclosed in the Burnet provisional application because claim 47 does not admit conjugate wherein the NSAID moiety is attached at the desosamine C-2' position (on S^1) or through a $>C=N-R_M$ moiety. When the macrolide linkage is through the macrolide 9a-nitrogen (Z is $-N(R_N)$ and W is $-CH_2$), claim 47 excludes the NSAIDs meclofenamic acid or ibuprofen. Therefore, claim 47 would not have been anticipated by the Burnet provisional application, even if it had been available as a reference.

Anticipation requires that each and every element of the rejected claim be disclosed in a single prior art reference. See, M.P.E.P. § 2131. Every element of the claimed invention must be literally present, arranged as in the claim. *Perkin Elmer Corp. v. Computervision Corp.*, 732 F.2d

888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984). A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Since each element of claim 47 is not provided in a prior art reference, this claim is not anticipated.

35 U.S.C. §103

The Examiner has rejected claims 8 - 30 under 35 U.S.C. §103(a) as being unpatentable over Burnet et al. (US 2004/0087517), stating that a person of ordinary skill in the art would have been motivated to choose specific NSAIDS and link them to erythromycin derivatives because Burnet teaches that such linkage improves ease of formulation, gastric stability, bioavailability, etc.

The rejection is respectfully traversed, and reconsideration is requested. Therefore Applicants respectfully request reconsideration and withdrawal of this rejection.

The Burnet '517 document has been overcome as a reference under 35 U.S.C. § 102 by the present showing of prior invention. Therefore, it is similarly not available under 35 U.S.C. § 103.

Independently, Burnet cannot be used to show that a person of ordinary skill in the art would have been motivated to link the NSAIDS and erythromycin derivatives to form the conjugates of the presently claimed invention and is therefore unavailable as a reference under this section.

The difference in scope of the compounds covered by this claim are not made obvious by Burnet since Burnet teaches away from modifying the compounds he discloses to obtain any other compounds including closely related compounds. Burnet states "similar molecules with similar properties can exhibit quite different uptake into immune cells, hence the difficulty in employing general specifications known in the art" (para. 0728), teaching away from departures from the structure of specific compounds disclosed therein. Burnet does not indicate anywhere in the provisional application, and therefore does not teach, any locations that are useful for linking the macrolide conjugate to NSAIDs other than the ones particularly disclosed in the examples. Burnet

also does not teach what modifications can be made on the substituents on the macrolide ring in order to obtain a useful compound. Instead, Burnet indicates that an "empirical method is the only reliable means of selecting and guiding synthetic chemistry" towards the conjugate compounds. (para. 0729). This is insufficient to suggest each the modifications described in the present invention, and instead constitutes a negative teaching.

Applicants submit that the presently claimed conjugates are not prima facie obvious over the teaching of Burnet. It is not obvious to conjugate the particular circumscribed class of macrolides as claimed to the claimed NSAIDS based on the teachings of Burnet since Burnet teaches that "similar molecules with similar properties can exhibit quite different uptake into immune cells, hence the difficulty in employing general specifications known in the art" (para. 0728). Burnet does not disclose any macrolide-NSAID conjugates other than 15 conjugates in the provisional application and the 8 additional compounds in the published application, and does not teach how to obtain the macrolide-NSAID conjugates as claimed in the present invention that have uptake into immune cells. Present claims 8 - 30 do not encompass the disclosed Burnet compounds and are not obvious because there is no teaching to suggest the modifications to provide conjugates having the macrolides attached to the particularly claimed NSAIDs at the linkage sites described in the present invention.

Accordingly, in view of the amendments and arguments set forth above, it is respectfully submitted that the claimed subject matter would not have been obvious to one of ordinary skill in the art over Burnet. Applicants respectfully request that the rejections be withdrawn.

In view of the above arguments, the pending claims in this application are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to enter this Amendment, and to pass this application to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: January 3, 2006

Respectfully submitted,

By _____

Lydia Gayle Olson
Registration No.: 48,487
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant